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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/893,346 | 06/28/2001 | Wayne D. Comper | 48643-015 | 2638 |

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| EXAMINER | |
|---|---|
| CHEN, STACY BROWN | |
| ART UNIT | PAPER NUMBER |
| 1648 | |

DATE MAILED: 06/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/893,346 | COMPER, WAYNE D. | |
| | Examiner | Art Unit | |
| | Stacy B. Chen | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-5,7-14,16,17,20,22,23,25 and 26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-14,16,17,20,22,23,25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 September 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Applicant's amendment filed March 11, 2005 is acknowledged and entered. Claims 1-5, 7-14, 16, 17, 20, 22, 23 and 25-26 are pending and examined.

2. The objections to claim 2 for various typographical errors are withdrawn in view of Applicant's amendment. The rejection of claims 18 and 24 under 35 U.S.C. 103(a) as being unpatentable over Trevisan in view of Jain *et al.* (4,330,296) and Suzuki *et al.* (5,246,835), is moot in view of the cancellation of claims 18 and 24.

### *Claim Rejections - 35 USC § 112*

3. (*New Rejection*) New claim 26 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. New claim 26 is directed to the detection of non-immunoreactive protein with an antibody. The specification does not demonstrate possession of such an antibody at the time of the invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a function. There is not even identification of any particular portion of the antibody structure

that must be conserved from the "conventional" antibody. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Given that Applicant's non-immunoreactive protein was not detected at certain levels with conventional antibodies at the time of the invention, Applicant is claiming a yet-to-be-discovered antibody. The structure of such an antibody is not known, nor is the exact structure of the non-immunoreactive protein. The epitopes and the paratopes are not described, only a function is provided. It is clear that HPLC is able to detect urinary albumin, including immunoreactive and non-immunoreactive forms of the protein, however, Applicant has not provided the structure of an antibody that binds the "non-immunoreactive" protein(s).

The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of antibodies, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. One cannot describe what one has not conceived. Therefore, Applicant has only demonstrated possession of a method of detecting urinary albumin (intact modified albumin) with HPLC.

4. Claim 2 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant arguments have been fully considered but fail to persaude. The rejection of claims 13, 14, 18 and 24 under 35 U.S.C. 112, second paragraph are either moot in

view of cancellation, or withdrawn in view of Applicant's amendment. The remaining claim that stands rejected under 35 U.S.C. 112, second paragraph, are addressed below.

Claim 2, the term "drug abuse" is relative since there is no clear distinction, for example, between a person using drugs for a medical condition and a person using drugs for a perceived medical condition that does not actually exist. Applicant argues that the term is art-accepted and means, "habitual use of drugs not needed for therapeutic purposes", according to Stedman's Medical Dictionary. In response, the Office has considered the definition of the term, "drug abuse", and maintains that it is a relative term. The habitual use of drugs not needed for therapeutic purposes is a definition that is adequate for the general medical public, but is not adequate to meet the requirements of 112 second paragraph. Caffeine is a drug that people habitually use although they have no therapeutic need for it, yet one of skill in the art may or may not consider consumption of caffeinated coffee or tea to be drug abuse. Since the meaning of drug abuse will vary from medical expert to medical expert, rendering it indefinite, the metes and bounds of "drug abuse" cannot be determined with certainty.

***Claim Rejections - 35 USC § 102 and 103***

5. Claims 1-5, 7-14, 16-17, 20, 22 and 23 and new claim 25 are rejected under 35 U.S.C. 102(b) as anticipated by Trevisan *et al.*, of record, for reasons of record.

The claims are drawn to a method for treating a person with renal disease/complications comprising administration of an agent, assaying a body fluid sample for presence, absence or decreasing amount of a particular protein over time. The assay indicates whether or not the agent is therapeutically effective. The renal disease/complication can be selected from a host of

commonly known conditions selected from claim 2. The treatment agents are lysosome-activating compounds such as ACE inhibitors (ramipril). The protein assayed for can be any protein from claim 7. Claims 16-17 are drawn to limitations wherein the assaying is by chromatography (HPLC).

Trevisan discloses the effect of low-dose ramipril on microalbuminuria in type-2 diabetic patients over a period of six months (abstract). Urinary albumin concentrations were measured by radioimmunoassay. Glycosylated hemoglobin concentrations were determined via HPLC (page 877, col. 2, last paragraph). The prior art teaches that albumin and other proteins can be detected by RIA and HPLC. Applicant's intact modified albumin has been modified biochemically with respect to native protein either by minor enzyme mediated modification or addition to its basic structure, and/or physically through a change in its three dimensional structure so that it escapes detection by conventional means. Applicant points out that a commercially available antibody may be specific for a particular epitope on a native protein that is no longer present on the intact modified form of the protein. However, if an intact modified form of the protein was modified in such a way that it escaped detection by one type of antibody, it does not necessarily follow that the intact modified form will not be detected by another conventional antibody. In other words, if the commercially available antibody detects an epitope on the intact modified form of the protein that remains after modification, the intact modified form of the protein would have been detected by the "conventional" antibody even though it actually was intact modified protein. One would not realize that an intact modified protein had been detected, although such a protein was in fact detected. Trevisan would have inherently detected both forms of albumin: native and modified intact albumin. Therefore, lacking method

steps that indicate how intact modified protein is detected apart from native protein, the claims are anticipated by Trevisan.

Applicant's arguments have been fully considered but fail to persuade. Applicant's substantive arguments are directed primarily to those presented in the Declaration of Dr. Wayne Comper, filed October 4, 2004. The arguments are addressed below.

***Declaration of Dr. Wayne Comper under 37 CFR 1.132***

6. The declaration of Dr. Wayne Comper, filed October 4, 2004 has been fully considered, but fails to persuade withdrawal of the art rejections of record.

- Points 1 and 2 identify Dr. Comper and his familiarity with the instant application and the Office action of June 30, 2004.
- Point 3 summarizes the state of the art regarding detection of albumin. Dr. Comper begins by stating that until recently, albumin found in urine was expected to be immunologically the same as that present in plasma. Dr. Comper states that he is not aware of antibodies that been raised to urinary albumin, nor their use in detection and measurement of urinary albumin. Dr. Comper discloses that he has discovered a non-immunoreactive form of albumin that is not measured by conventional assays. Dr. Comper states that he has demonstrated that the amount of albumin in urine detected by HPLC is much higher than that detected in immunoassay using commercially available antibodies. Dr. Comper points to the FDA's labeling of the Accumin™ HPLC assay, which reports that the HPLC technology will, depending on the

specimen, report greater urinary albumin values when compared to immunochemical urinary albumin test systems and dipstick systems.

- In response, the Office acknowledges that HPLC is able to detect more urinary albumin, depending on the specimen, than "conventional" assays that use antibodies only. However, the problem is that the claims do not clearly reflect Applicant's invention. Applicant's claims are not specific enough to overcome the teachings of Trevisan. Applicant's claims are broad enough to encompass Trevisan's antibodies that detect urinary albumin. Note that the claims do not recite an amount of urinary albumin that is detected.

- Points 4-6 discuss the results of an experiment where known antibodies to albumin were tested against urinary albumin to determine whether anti-human serum albumin antibodies detect or cross-react with modified urinary albumin. Of the antibodies that were tested, two were found to cross-react with urinary albumin. However, these two positives are attributed to contamination.

  - In response, the test results have been considered. The Office notes that in Dr. Comper's experiment, reactivity values of less than 10% were considered to have no cross-reactivity. While the Office acknowledges that experimental values must have cut-off points, the claims do not acknowledge such cut-off points. The claims broadly encompass a method of detecting urinary albumin by immunoassay. If an intact modified form of the protein was modified in such a way that it escaped detection by one type of antibody, it does not necessarily follow that the intact modified form will not be detected by

another conventional antibody. In other words, if the commercially available antibody detects an epitope on the intact modified form of the protein that remains after modification, the intact modified form of the protein would have been detected by the "conventional" antibody even though it actually was intact modified protein. One would not realize that an intact modified protein had been detected, although such a protein was in fact detected. Trevisan would have inherently detected both forms of albumin: native and modified intact albumin. Applicant argues that Trevisan's antibody would not have detected as much urinary albumin as Applicant's method. However, the claims do not recite any limitations regarding amounts of urinary albumin detected. Therefore, the claims remain rejected for failing to distinguish over the prior art.

***Conclusion***

7. No claim is allowed. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James C. Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Stacy B. Chen
May 17, 2004

James C. Housel 5/31/05
JAMES HOUSEL
SUPERVISORY PATENT EXAMINER
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